

**Phase 2 Study of Androgen Deprivation Therapy (ADT) plus Chemotherapy as Initial Treatment  
for Local Failures or Advanced Prostate Cancer**

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**Androgen Deprivation Therapy (ADT) plus Chemotherapy as Initial Treatment for Local Failures  
or Advanced Prostate Cancer**

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The study is to be conducted according to the protocol and in compliance with Good Clinical Practice (GCP) and other applicable regulatory requirements.

Signature: \_\_\_\_\_  
Robert J. Amato, D.O.

Date: \_\_\_\_\_

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## PROTOCOL SYNOPSIS

### PROTOCOL

#### Androgen Deprivation Therapy (ADT) plus Chemotherapy as Initial Treatment for Local Failures or Advanced Prostate Cancer

### PRINCIPAL INVESTIGATOR

Robert J. Amato, D.O.

### OBJECTIVES

#### Primary Objective:

- Assess the clinical benefit as measured by time to tumor progression of androgen deprivation therapy (ADT) plus chemotherapy based on tumor burden, applied to previously untreated patients with local failures or patients who were not candidates for prostatectomy or radiation therapy.

#### Secondary Objective:

- Soft tissue objective response rate
- Measure of PSA response
- Time to PSA progression
- Overall survival
- Quality of life measure

### PATIENT SELECTION

- Pathologic proof of adenocarcinoma of the prostate.
- Patients must belong to one of the following subsets:
  - **Prior local therapy**
    - Patients with PSA recurrence following prostatectomy or radiation therapy who have no radiographic involvement. PSA doubling time  $\leq 6$  months.
    - Nodal involvement only.
    - Low volume bone disease:  $\leq 3$  metastases.
    - Nodal involvement with associated bone involvement.
    - High volume bone/visceral disease: Patients with  $>3$  metastatic bone sites or visceral metastases.
  - **No prior definitive local therapy**
    - Tumors felt to be unresectable, not candidates for radiation therapy, and PSA elevated with biopsy-proven disease.
    - Metastatic disease at presentation.

- Patients may have started ADT within 3 months of study entry.
- No previous cytotoxic therapy is allowed, including systemic irradiation with strontium-89, samarium, or radium-223.
- Previous definitive radiotherapy to one metastatic site is acceptable, provided that unirradiated sites remain. At least 8 weeks must have elapsed since radiation therapy to the pelvis. Patients having limited irradiation of a metastatic site are eligible 4 weeks following radiation.
- Patients may have had previous exposure to ADT if it was given for  $\leq 6$  months to "downstage" the primary and provided that such therapy was completed at least 12 months prior to entry into this study with a return of serum testosterone to  $\geq 200$  ng/dL.
- Patients must be free of serious comorbidity and have a life expectancy of  $\geq 3$  years.
- Patients must have adequate physiologic reserves as evidenced by:
  - Eastern Cooperative Oncology Group (ECOG) status of  $\leq 2$ .
  - Patients must have adequate bone marrow function: Platelets  $\geq 100,000$  cells/mm<sup>3</sup>, Hemoglobin  $\geq 9.0$  g/dL, and ANC  $\geq 1,500$  cells/mm<sup>3</sup>.
  - Patients must have adequate renal function: creatinine  $\leq 2 \times$  upper limit of normal (ULN).
  - Patients must have adequate liver function: AST/ALT  $\leq 2.5 \times$  ULN; alkaline phosphatase  $< 2.5 \times$  ULN, unless bone metastasis is present in the absence of liver metastasis; and bilirubin  $< 2.5 \times$  ULN or 1.5 mg/dL.
  - No evidence of active ischemia on ECG and documentation of EF  $\geq 50\%$ .

#### **Exclusion criteria**

- Patients must not have a second malignancy unless there is confidence of previous curative therapy.
- Patients with a recent history of TIA (within 6 months), who are requiring regular antianginal therapy, or who are having claudication sufficient to limit activity are not eligible. Patients with a previous history of deep venous thrombosis or pulmonary embolism (within 12 months) are not eligible.
- Patients must not have a serious intercurrent medical or psychiatric illness, including serious active infection.
- Patients must not have sensory neuropathy  $>$  grade 1.

#### **TREATMENT PLAN:**

Treatment will be ADT plus chemotherapy.

- ADT plus chemotherapy

Patients will be treated with degarelix plus chemotherapy for three, four, or five 8-week cycles

according to their tumor burden. Each cycle of chemotherapy will consist of 6 weeks of chemotherapy and 2 weeks of rest. Patients may already be medically castrated at the time of study entry, provided such therapy was started within 3 months of initiating chemotherapy. For the patients who are on anti-androgen therapy before initiating chemotherapy, the anti-androgen therapy will be discontinued.

- Chemotherapy

Patients will receive three, four, or five 8-week cycles of chemotherapy (6 weeks of chemotherapy followed by 2 weeks of rest). In weeks 1, 3, and 5, patients will receive doxorubicin (20 mg/m<sup>2</sup> as a 24-hour intravenous infusion on day 1 of each applicable week) and ketoconazole (400 mg orally 3 times daily for 7 days); in weeks 2, 4, and 6, patients will receive docetaxel (35 mg/m<sup>2</sup> intravenously on day 1 of each applicable week) and estramustine (280 mg orally 3 times daily for 7 days).

Maintenance hydrocortisone (20 mg morning and 10 mg afternoon) will be administered daily throughout chemotherapy to counteract potential ketoconazole-induced adrenal complications.

- Androgen Deprivation Therapy

Patients will be treated with degarelix.

Patient Tumor Burden	Treatment Schedule
Definitive local therapy: Patients with PSA recurrence following prostatectomy or radiation therapy who have no radiographic involvement.	3 cycles of chemotherapy + 12 months of androgen deprivation therapy
Nodal involvement only.	4 cycles of chemotherapy + 18 months of androgen deprivation therapy
Low-volume bone disease: Patients with $\leq 3$ bone metastases.	4 cycles of chemotherapy + 18 months of androgen deprivation therapy
Nodal involvement with associated bone involvement	5 cycles of chemotherapy + 24 months of androgen deprivation therapy
High-volume bone/visceral disease: Patients with $>3$ metastatic bone sites or visceral metastases.	5 cycles of chemotherapy + 24 months of androgen deprivation therapy
No prior definitive local therapy: Tumors felt to be unresectable, not candidates for radiation therapy, and PSA elevated with biopsy-proven disease.	5 cycles of chemotherapy + 24 months of androgen deprivation therapy

Agent				Dose and Schedule			
<u>Chemotherapy</u>				8-week cycle of chemotherapy			
Doxorubicin (ADRIA)				20 mg/m <sup>2</sup> CIV over 24 h on days 1, 15, 29			
Ketoconazole (KETO)				400 mg p.o. t.i.d. on days 1-7, 15-21, 29-35			
Docetaxel (TAXOT)				35 mg/m <sup>2</sup> IVPB on days 8, 22, 36			
Estramustine (EMCYT)				280 mg p.o. t.i.d. on days 8-14, 22-28, 36-42			
Hydrocortisone				20 mg p.o. a.m. & 10 mg p.o. p.m. EVERY DAY			
No cytotoxic therapy				Days 43-56 (hydrocortisone continues)			
Week	ADRIA KETO 1↓	TAXOT EMCYT 2↓	ADRIA KETO 3↓	TAXOT EMCYT 4↓	ADRIA KETO 5↓	TAXOT EMCYT 6↓	i.v. (weekly) p.o. (3 times daily)
<u>Androgen Deprivation Therapy</u>				Degarelix (starting week 1)			

## STATISTICAL CONSIDERATIONS:

This study is intended to determine the efficacy of determining chemotherapy dose based on tumor burden. Time to tumor progression (TTP) is the primary endpoint. The study is designed to have at least 80% power to detect at least a 4-month increase in the median TTP found in the literature (16-24 months, two-sided type I error of 0.05), with an exponential distribution. We plan to enroll 224 patients, assuming uniform accrual over time, no loss to follow-up, exponentially distributed death times, and the use of the exponential MLE test.

Each group will be examined separately in an independent post-hoc subgroup analysis using descriptive statistics. TTP may vary among treatment subgroups. The median PFS will be constructed for each subset. The 95% confidence intervals will describe the reliability of our results.

An interim safety analysis is planned after 56 patients (25%) have completed the first cycle of treatment. During this analysis, enrollment will be stopped, the DSMB will review the safety and toxicity information and make their recommendation, and the DSMB report will be given to the IRB for review prior to treatment of additional patients. For the interim analysis, the alpha spending function with O'Brien-Fleming type boundaries will be used to preserve the overall type I error rate for safety and effectiveness at the 0.025 level.

## PATIENT EVALUATION:

### ALL SIX SUBSETS

- Complete history and physical examination.
- MRI of the pelvis.
- Complete metabolic panel, electrolytes, CBC with differential and platelet count, testosterone, and



PSA. Imaging studies to consist of x-ray or CT of the chest, CT or MRI of the abdomen, and bone scan. Blood tests must be obtained within 7 days of study entry and imaging studies within 28 days. Additional diagnostic studies, ECG, and echocardiogram must have been obtained within the preceding 6 months.

- A CBC with differential and platelet count is required prior to each dose of chemotherapy. The PSA will be determined prior to each subsequent cycle. Once chemotherapy is completed, monitoring will continue as described below. Additional ECG and echocardiograms will be obtained before each course of chemotherapy.
- Following the completion of chemotherapy, for all patients, PSA will be monitored every 12 weeks, and every patient will have a clinical evaluation including a CBC with differential and platelet count, complete metabolic panel, electrolytes, and testosterone level.
- Once the PSA response is maximal, patients will have a repeat bone scan if the initial result was suggestive of metastatic disease. If a patient was known to have abnormalities on other imaging studies at entry, these will be repeated in order to document the full extent of response.
- If the PSA is rising, a repeat determination to confirm an upward PSA trend will be obtained in 2 weeks. Although repeat imaging studies may help in cases with an equivocal clinical presentation, there is no mandate to monitor patients except by PSA, serum chemistries, electrolytes, hematologic evaluation, and testosterone level.

#### **FOR PATIENTS WITHOUT PRIOR SURGERY OR RADIATION THERAPY**

- At month 12, patients will undergo a biopsy of the prostate to determine whether there are viable tumor cells. If viable cells are present, patients will be referred for radiation therapy as described in section 7.0.

## PROTOCOL

### 1.0 OBJECTIVES

#### Primary Objective:

- Assess the clinical benefit as measured by time to tumor progression of ADT plus chemotherapy based on tumor burden, applied to previously untreated patients with local failures or patients who were not candidates for prostatectomy or radiation therapy.

#### Secondary Objective:

- Soft-tissue objective response rate
- Measure of PSA response
- Time to PSA progression
- Overall survival
- Quality of life measure

### 2.0 BACKGROUND

#### 2.1 Androgen Deprivation Therapy in Prostate Cancer

Prostate cancer is expected to be diagnosed in 238,590 men in the United States in 2013, and 29,720 men are expected to die from it.<sup>1</sup> Androgen deprivation therapy (ADT) is commonly used for the management of patients who develop an increasing serum prostate-specific antigen (PSA) level after prostatectomy or radiation therapy. For the management of prostate cancer where localized therapy is not an option, ADT is the first-line therapeutic approach. The prostate cancer mortality rate reflects the failure of ADT, which eventually occurs in virtually all patients. Despite its essentially palliative and short-lasting effects, ADT remains the most common therapy for local failure or for men who were not candidates for local therapy. The estimated median time to treatment failure is 16-24 months.<sup>2</sup> Alternatives such as salvage radiation therapy after failed prostatectomy<sup>3,4</sup> and salvage therapy<sup>5</sup> have been tried but still fall short in terms of clinical benefit.

Evidence suggests that PSA levels correspond with clinical disease progression or response to therapy, although the magnitude of PSA values indicative of clinically significant improvement and the exact relationship between rising PSA levels and tumor burden remains undefined.<sup>6</sup> Rising PSA levels often precede symptomatic progression by 5 months.<sup>7</sup> Elevations can predict clinical relapse in patients who had a prostatectomy or radiation therapy, and PSA doubling times after initial treatment may identify and stratify patients at high risk of prostate cancer-specific death.<sup>8-10</sup>

However, clinical pathological evidence shows that long-term ADT is associated with adverse effects that have a major impact on patients' quality of life. These include fatigue, vasomotor flushing, loss of libido, cognitive dysfunction, decreased bone mineral density, loss of muscle mass, and mild anemia.<sup>11,12</sup> Long-term ADT can also result in diabetes mellitus, cardiac disease, and metabolic syndrome.<sup>13-18</sup> Studies have sought strategies to reduce these sequelae, including intermittent and short-term (4-6 months) administration, are effective at decreasing prostate cancer-related mortality while minimizing adverse effects.<sup>19-21</sup>

##### 2.1.1. Rationale for use of degarelix

Our previous studies used leuprolide for ADT.<sup>22,23</sup> However, this project will use degarelix, a gonadotropin-releasing hormone receptor inhibitor. Degarelix shows to suppress testosterone

more quickly than leuprolide and to cause milder adverse events. Degarelix has a favorable effect on PFS and does not require the addition of an androgen receptor inhibitor (such as bicalutamide).<sup>12,24-26</sup>

## **2.2 Chemotherapy in Prostate Cancer**

### **2.2.1 Castration-resistant prostate cancer**

Chemotherapy in castration-resistant prostate cancer provides PSA reduction and prolongs overall survival (OS). Several combination regimens have produced PSA response rates of ~50%. Two of the more effective regimens are ketoconazole plus weekly doxorubicin<sup>27</sup> and estramustine plus weekly vinblastine.<sup>28</sup> Alternating administration of ketoconazole plus doxorubicin with estramustine plus vinblastine was reported as safe and possibly enhancing OS.<sup>29</sup> After the development of taxanes, docetaxel was found to have strong activity against advanced prostate cancer.<sup>30,31</sup> In 2004, it became the standard of treatment.<sup>32</sup>

### **2.2.2 Hormone-sensitive prostate cancer**

The present trial builds upon the results of a retrospective review<sup>22</sup> and a prospective study<sup>23</sup> by members of our research group that used the same treatment regimen of doxorubicin with ketoconazole and docetaxel with estramustine, with the treatment regimen updated to reflect the current docetaxel standard. In the previous prospective study, 46 patients were enrolled, 45 of whom were evaluable. Median progression-free survival (PFS) was 23.4 months, and median overall survival (OS) was 53.7 months. Of the 45 patients with measurable disease, 22 had an objective response: 9 achieved a complete response, 2 achieved a partial response, and 10 had stable disease. Frequent grade 3 adverse events included elevated ALT (17%), hypokalemia (13%), and hypophosphatemia (13%). Grade 4 adverse events were rare and included low bicarbonate (2%), hypokalemia (2%), leukocytopenia (2%), and neutropenia (2%). The treatment demonstrated clinical benefit in all patient subsets with minimal reversible treatment-related adverse events.<sup>23</sup>

To further validate the use of combined chemotherapy and ADT in hormone-sensitive prostate cancer, Eastern Cooperative Oncology Group researchers conducted a multicenter phase III study among 790 men with hormone-sensitive, newly metastatic prostate cancer. They found that the combination of ADT and docetaxel substantially increased the length of overall survival, particularly in men with highly metastatic disease, without notable toxicity.<sup>33</sup> Based on the results of that trial, the concept of hormone therapy plus chemotherapy has become the recommended standard for prostate cancer treatment.

Another recent study explored the safety of combined ADT and chemotherapy in a similar patient population to ours. Although patients receiving the combination experience more serious adverse events than those receiving ADT only (25% vs. 9.8%), numbers of patients completing treatment were similar in both groups (87% vs. 89%), so they determined that the combination regimen is safe and feasible.<sup>34</sup>

## **2.3 Rationale for the Present Trial**

Some reports have addressed the potential clinical benefit of chemotherapy in hormone-responsive prostate cancer.<sup>35-37</sup> The early application of chemotherapy to androgen-dependent prostate cancer cells may have clinical benefit, given that the tumor burden would be minimal. Androgen-independent clones that have already started proliferating and transforming the tumor into a more hormone-resistant phenotype would be treated while, simultaneously, the androgen-sensitive cells would be treated by ADT.

As a working hypothesis, we suspect that the transformation from an androgen-dependent to an androgen-independent phenotype is mediated by expansion of an androgen-independent clone already

present at the time of ADT that continues to grow while androgen-sensitive clones are being suppressed. It is thus desirable to bring treatment to bear on the androgen-independent component while the corresponding tumor burden remains minimal and prolong the time to hormone resistance. We view the androgen-independent component as analogous to "microscopic residual" or "micro-metastatic" disease, for which adjuvant chemotherapy has been shown to be effective in other contexts, even when the same drugs had little or no impact on survival in the setting of more advanced disease.

By treating all components of the tumor initially, we anticipate that the emergence of androgen-independent growth will be delayed, ultimately prolonging patient survival. Additionally, instead of treating patients empirically with an identical regimen, as in our previous work, our patient subsets were designed to ensure a level of treatment appropriate to their individual disease, thus potentially lessening the burden of treatment (such as the long-term adverse effects of ADT). We have chosen 3, 4, or 5 cycles of chemotherapy to be administered on the basis of tumor burden, a treatment selection method long established in germ cell tumors and used by our PI.<sup>38,39</sup> Subanalyses of previous data,<sup>23</sup> have raised the concern that treating patients with varying levels of disease the same way does not produce optimal results. Therefore, we seek to improve outcomes by tailoring treatment to tumor burden. In our study, patients with less tumor burden will receive 3 cycles of chemotherapy and 12 months of ADT, those with moderate tumor burden will receive 4 cycles and 18 months of treatment, and those with the greatest tumor burden will receive 5 cycles and 24 months of treatment. Additionally, our regimen of administering treatment sequentially, including a 2-week break, reduces toxicity.

### 3.0 PATIENT SELECTION

#### 3.1 Inclusion Criteria

3.1.1 Pathologic proof of adenocarcinoma of the prostate. Patients with other histologic subtypes, such as pure ductal (e.g., "endometrioid" or "cribriform" histology) or any component of small cell carcinoma are not eligible. Patients must have metastatic disease or locally advanced disease that either is not appropriately treated with surgery or radiation or has recurred following previous "definitive" local therapy. Biopsy of indicator lesions is not required when the clinical presentation is characteristic. For example, a patient with visceral involvement without high- volume bone disease, especially in the setting of only modest PSA elevation, should be biopsied to exclude a variant histology. Pathologic samples must be available for review.

3.1.2 Patients must belong to one of the following subsets:

- **Prior local therapy**
  - Patients with PSA recurrence following prostatectomy or radiation therapy who have no radiographic involvement. PSA doubling time of  $\leq 6$  months.
  - Nodal involvement only.
  - Low-volume bone disease:  $\leq 3$  metastases.
  - Nodal involvement with associated bone involvement.
  - High-volume bone/visceral disease: patients with  $>3$  metastatic bone sites or visceral metastases.
- **No prior definitive local therapy**
  - Tumors felt to be unresectable, not candidates for radiation therapy, and PSA elevated with biopsy-proven disease.
  - Metastatic disease at presentation.

- 3.1.3 Patients may already be medically castrated at the time of study entry, provided that such therapy was started within 3 months of study entry.
- 3.1.3 No previous cytotoxic systemic therapy of any kind is allowed, including systemic irradiation with strontium-89, samarium, or radium-223.
- 3.1.4 Previous definitive radiotherapy to one metastatic site is acceptable. At least 8 weeks must have elapsed since radiation therapy to the pelvis. Patients having limited irradiation of a single metastatic site are eligible 4 weeks after the completion of radiation.
- 3.1.5 Patients may have had previous exposure to ADT if it was given for  $\leq 6$  months to "downstage" the primary tumor and provided that such therapy was completed at least 12 months prior to study entry with a return of serum testosterone to  $\geq 200$  ng/dL.
- 3.1.6 Patients must be free of serious comorbidity and have a life expectancy of  $\geq 3$  years.
- 3.1.7 Patients must have adequate physiologic reserves as evidenced by:
- Eastern Cooperative Oncology Group (ECOG) status of  $\leq 2$  (Appendix B).
  - Patients must have adequate bone marrow function: platelets  $\geq 100,000$  cells/mm<sup>3</sup>, hemoglobin  $\geq 9.0$  g/dL, and ANC  $\geq 1,500$  cells/mm<sup>3</sup>.
  - Patients must have adequate renal function: creatinine  $\leq 2 \times$  ULN.
  - Patients must have adequate liver function: AST/ALT  $\leq 2.5 \times$  ULN; alkaline phosphatase  $< 2.5 \times$  ULN, unless bone metastasis is present in the absence of liver metastasis; and bilirubin  $< 2.5 \times$  ULN or 1.5 mg/dl.
  - No evidence of active ischemia on ECG and documentation of EF  $\geq 50\%$
  - Patients must not have a second malignancy unless there is confidence of previous curative therapy.

### **3.2 Exclusion Criteria:**

- 3.2.1 Patients must not have a second malignancy unless there is confidence of previous *curative* therapy.
- 3.2.2 Patients with a recent history of TIA (within 6 months), are requiring regular antianginal therapy, or are having claudication sufficient to limit activity are not eligible. Patients with a previous history of deep venous thrombosis or pulmonary embolism (within 12 months) are not eligible.
- 3.2.3 Patients must not have a serious intercurrent medical or psychiatric illness, including serious active infection.
- 3.2.4 Patients must not have sensory neuropathy  $>$  grade 1.

## **4.0 TREATMENT PLAN**

Treatment will be ADT plus chemotherapy.

### **4.1 ADT plus Chemotherapy**

Patients will be treated with monthly degarelix plus chemotherapy for three, four, or five 8-week cycles. Each cycle of chemotherapy will consist of 6 weeks of chemotherapy and 2 weeks of rest. Patients may already be medically castrated at the time of study entry, provided that such therapy was started within 3 months of initiating chemotherapy. For the patients who are on anti-androgen therapy before initiating chemotherapy, the anti-androgen therapy will be discontinued. This regimen is summarized below.

## 4.2 Chemotherapy

Patients will receive three, four, or five 8-week cycles of chemotherapy (6 weeks of chemotherapy followed by 2 weeks of rest). In weeks 1, 3, and 5, patients will receive doxorubicin (20 mg/m<sup>2</sup> as a 24-hour intravenous infusion on day 1 of each applicable week) and ketoconazole (400 mg orally 3 times daily for 7 days); in weeks 2, 4, and 6, patients will receive docetaxel (35 mg/m<sup>2</sup> intravenously on day 1 of each applicable week) and estramustine (280 mg orally 3 times daily for 7 days).

Maintenance hydrocortisone (20 mg morning and 10 mg afternoon) will be administered daily throughout chemotherapy to counteract potential ketoconazole-induced adrenal complications.

## 4.3 Androgen Deprivation Therapy

Patients will be treated with monthly degarelix.

Agent				Dose and Schedule			
<u>Chemotherapy</u>				8-week cycle of chemotherapy			
Doxorubicin (ADRIA)				20 mg/m <sup>2</sup> CIV over 24 h on days 1, 15, 29			
Ketoconazole (KETO)				400 mg p.o. t.i.d. on days 1-7, 15-21, 29-35			
Docetaxel (TAXOT)				35 mg/m <sup>2</sup> IVPB on days 8, 22, 36			
Estramustine (EMCYT)				280 mg p.o. t.i.d on days 8-14, 22-28, 36-42			
Hydrocortisone				20 mg p.o. a.m. & 10 mg p.o. p.m. EVERY DAY			
No cytotoxic therapy				Days 43 to 56 (hydrocortisone continues)			
Week	ADRIA KETO 1↓	TAXOT EMCYT 2↓	ADRIA KETO 3↓	TAXOT EMCYT 4↓	ADRIA KETO 5↓	TAXOT EMCYT 6↓	i.v. (weekly) p.o. (three times daily)
<u>Androgen Deprivation Therapy</u>				Degarelix			

## 4.4 Prophylaxis against DVT

The association between cancer, chemotherapy (particularly estramustine), and venous thromboembolic events is long established.<sup>40,41</sup> It has been shown that patients with cancer—including prostate cancer—have up to a 7-fold greater risk of thrombosis than those without cancer.<sup>42,43</sup> Warfarin (1 mg) is given during chemotherapy as prophylaxis against thrombosis.<sup>44-48</sup>

## 4.5 Logistic Details Related to Therapy Delivery



- Doxorubicin will be given as a prolonged infusion of 24 hours. Given by prolonged infusion, it must be given into a central line.
- Ketoconazole must be taken with an acidic gastric environment.<sup>27</sup> Patients are to take ketoconazole 1 h before or 2 h after eating. Gastrointestinal upset is the most common side effect of ketoconazole, and many pharmacies dispense the drug labeled -TAKE WITH FOOD. Patients should be alerted to this. Compliance with the requirement for taking ketoconazole apart from meals will be verified at each clinical evaluation. Also, the over-the-counter availability of gastric acid secretion inhibitors such as omeprazole, cimetidine, ranitidine, and famotidine make it imperative to ask specifically about use of these agents, which some patients may not consider -drugs.
- Docetaxel is given IVPB over 60 minutes.
- Patients will be pretreated with dexamethasone 4 mg p.o. b.i.d. 24 hours pre- docetaxel, day of docetaxel administration, and 24 hours post-docetaxel. Ondansetron 8 mg p.o. and diphenhydramine 25 mg i.v. 30 minutes prior to docetaxel infusion.
- Estramustine absorption is significantly reduced by calcium. Therefore, milk, milk products, and other calcium-rich food or drugs (especially calcium containing antacids) must not be taken concurrently with estramustine capsules.
- Since all of the drugs in this trial are standard of care, there may be instances when subjects will receive their treatment at other infusion centers as well as their standard blood draws due to insurance network provider determinations, cost, etc. Dr. Amato will work closely with referring physicians and infusion centers. The lab results and clinic/infusion notes will be obtained and reviewed by Dr. Amato. All subjects will still come to the cancer center for restaging study visits.

#### 4.6 Specific Treatment Plan According to Patient Subset

Patient Tumor Burden	Treatment Schedule
Definitive local therapy: Patients with PSA recurrence following prostatectomy or radiation therapy who have no radiographic involvement.	3 cycles of chemotherapy + 12 months of androgen deprivation therapy
Nodal involvement only.	4 cycles of chemotherapy + 18 months of androgen deprivation therapy
Low-volume bone disease: Patients with $\leq 3$ bone metastases.	4 cycles of chemotherapy + 18 months of androgen deprivation therapy
Nodal involvement with associated bone involvement	5 cycles of chemotherapy + 24 months of androgen deprivation therapy

High-volume bone/visceral disease: Patients with >3 metastatic bone sites or visceral metastases.	5 cycles of chemotherapy + 24 months of androgen deprivation therapy
No prior definitive local therapy: Tumors felt to be unresectable, not candidates for radiation therapy, and PSA elevated with biopsy-proven disease.	5 cycles of chemotherapy + 24 months of androgen deprivation therapy

## **5.0 PRE-TREATMENT EVALUATION**

### **5.1 Complete history and physical examination**

### **5.2 Laboratory evaluation**

- Complete metabolic profile
  - BUN, creatinine, alkaline phosphatase, ALT/AST, total bilirubin, LDH, calcium, albumin, glucose, magnesium, uric acid, phosphorous
- Electrolytes
  - Sodium, potassium, chloride, CO<sub>2</sub> content
- Hematology
  - CBC with differential, platelet count
  - PT, INR, PTT
- PSA
- Testosterone

### **5.3 Diagnostic Imaging**

- X-ray or CT of the chest
- Bone scan
- MRI or CT scan of the abdomen
- MRI of the pelvis

### **5.4 Additional Diagnostic Studies**

- ECG
- Echocardiogram

## **6.0 ON-STUDY EVALUATION**

These assessments should be performed within  $\pm 3$  days of the scheduled day of assessment.

- 6.1 A CBC with differential and platelet count will be required prior to each dose of chemotherapy. The biochemical profile will be required prior to each dose of chemotherapy. An ECG and echocardiogram will be obtained prior to each cycle of chemotherapy. The PSA will be repeated every 8 weeks. Once the 3, 4, or 5 cycles of chemotherapy are completed, monitoring will continue as described in Sections 6.2 and 6.3.



- 6.2 Following the completion of chemotherapy, for all patients, PSA will be monitored every 12 weeks, and every patient will have a clinical evaluation including a CBC with differential, platelet count, complete metabolic panel, electrolytes, and testosterone level.
- 6.3 Quality of life will be assessed using the FACT-P scale (Appendix A), a validated instrument specific to prostate cancer, after every cycle of chemotherapy, 12 weeks after the completion of chemotherapy, after the completion of ADT, and upon testosterone recovery to normal levels.<sup>46</sup>
- 6.4 Once the PSA response is maximal, patients will have a repeat bone scan if the initial study was suggestive of metastatic disease. Although not required for study eligibility, if a patient was known to have abnormalities on other imaging studies at entry, these should also be repeated in order to document the full extent of response.
- 6.5 If any PSA result is higher than the previous determination, then a repeat determination to confirm an upward trend will be obtained within 2 weeks. Repeat imaging studies may be done in cases with an equivocal clinical presentation, but there is no mandate to monitor patients except by clinical exam, PSA and serum chemistries, and hematologic evaluation.
- 6.6 The attending physician and/or the assigned oncology research staff must see each patient prior to drug administration. All required interim and pretreatment data should be available. Interim toxicity will be recorded at each treatment in accordance with the NCI Common Toxicity Criteria, Version 4.0, as listed in Appendix C.
- 6.7 At month 12, patients without surgery or radiation therapy will undergo a biopsy of the prostate to determine if there are viable cells. If viable cells are present, they will be referred for radiation therapy as described in the next section.
- 6.8 PSA will be assessed every 3 months for the first 2 years after the completion of the therapy program. PSA will be assessed every 6 months for the following 3 years and annually thereafter. Other follow-up measurements include MRI and bone scans at yearly intervals beginning when PSA elevation ( $>0.3$  ng/mL) is detected or earlier if clinically indicated, documentation of recurrence and survival. When applicable, follow-up may be assessed by medical record review, telephone call or review of the Social Security Index.

## **7.0 PROSTATE RADIATION THERAPY FOR THOSE WITH VIABLE CELLS**

These patients will receive image-guided intensity-modulated radiation therapy (IG-IMRT). A prescribed dose (76-80 Gy) will be delivered to the prostate in 2 Gy fractions over 38-40 fractions depending on bladder and rectal dose constraints. The patients will undergo CT simulation in the prone position with rectal balloon in place if tolerated, and a customized vacuum bag will be fabricated for optimal immobilization. An MRI will be obtained at the time of treatment planning and fused to the treatment planning CT. Dose constraints will be placed for important surrounding normal structures including rectum, bladder, and femoral heads according to established QUANTEC guidelines. Daily image guidance will be utilized, preferably via cone-beam CT. Patients will be monitored weekly for vital signs and side effects related to radiotherapy, including rectal and urinary symptoms.

## **8.0 TOXICITY CRITERIA ALTERATION OF THERAPY**

### **8.1 Hematologic Toxicity**

- 6.2 Following the completion of chemotherapy, for all patients, PSA will be monitored every 12 >75,000 in order to receive doxorubicin or docetaxel. If these counts are not obtained, treatment should be withheld for 1 week and counts rechecked. Neupogen can be administered as needed to increase platelet counts. When counts have recovered, treatment should resume with the drug that was due when therapy was suspended (i.e., docetaxel and doxorubicin will continue to alternate). Weeks 7 and 8 will be rest weeks no matter how many doses of chemotherapy were actually delivered in weeks 1-6.

If >1 week is required for cell counts recover, treatment will be resumed with doxorubicin at 15 mg/m<sup>2</sup> and docetaxel at 30 mg/m<sup>2</sup> (i.e., 25% reduction). This 25% dose reduction should also apply if a patient has a second or third treatment delay. If therapy is delayed more than 3 times or more than 3 weeks are required for cell count recovery, chemotherapy will be discontinued and the patient will proceed directly to androgen deprivation.

## 8.2 Specific Non-Hematologic Toxicities

- Patients unable to tolerate ketoconazole due to GI upset should be offered carafate, 1 g p.o. q.i.d., observing the convention of taking it 1 hour before or 2 hours after a dose of ketoconazole. If that is not helpful, ketoconazole should be reduced by 50% to 200 mg p.o. t.i.d. If patients still cannot tolerate ketoconazole, it will be discontinued. Such patients may continue with the rest of the regimen at the discretion of the treating physician.
- Patients with transaminases  $>4 \times \text{ULN}$  should discontinue ketoconazole until the transaminases are  $<2 \times \text{ULN}$ . Ketoconazole may be restarted at 200 mg p.o. t.i.d. at the discretion of the treating physician, with weekly liver enzyme monitoring.
- Patients developing a deep venous thrombosis or pulmonary embolism will have estramustine discontinued. They may continue on the remainder of the regimen at the discretion of the treating physician.
- Patients who have myocardial infarction or stroke will have all chemotherapy discontinued and proceed to androgen deprivation.
- After starting an antiandrogen, patients experiencing an increase in hepatic enzymes to  $>4 \times \text{ULN}$  will have the agent withdrawn for a month. If the patients had been on flutamide, it is suggested that bicalutamide or nilutamide be substituted. Patients unable to tolerate an alternative anti-androgen will be maintained on testicular suppression only.
- Other hepatotoxicities:
  - If a grade 1 increase in AST, ALT, or bilirubin occurs (e.g., increase in AST or ALT from ULN to  $2.5 \times \text{ULN}$  or increase in total bilirubin from ULN to  $1.5 \times \text{ULN}$ ), the frequency of liver function test monitoring should be increased if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
  - If a grade 2 increase in AST, ALT, or bilirubin occurs (e.g., AST or ALT to  $>2.5-5 \times \text{ULN}$  or total bilirubin to  $1.5-3 \times \text{ULN}$ ), the frequency of liver function test monitoring should be increased to at least once per week if the Investigator judges that the laboratory abnormalities are potentially related to study medication. No study treatment dose reduction is required.
  - If a grade 3 increase in AST, ALT, or bilirubin occurs (e.g., AST or ALT to  $>5 \times \text{ULN}$  or total bilirubin to  $>3 \times \text{ULN}$ ), hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations (at least once per week) should be conducted until liver function results return to baseline value

or grade 1. Liver enzymes should be measured immediately, regardless of when the next study visit or monitoring interval is scheduled.

- If study treatment resumption is considered for subjects who have experienced grade 3 increases in AST, ALT, or bilirubin, and the Medical Monitor agrees, resume study treatment with the first dose level reduction when grade 3 toxicities resolve to grade 1 or baseline.
  - If grade  $\geq 3$  increases in AST, ALT, or bilirubin recur after the first dose reduction, hold study medication and all other concomitant medications that are potentially hepatotoxic. Frequent laboratory evaluations should be conducted (at least once per week) until liver function results return to baseline value or grade 1. Liver enzymes should be measured immediately, regardless of when the next study visit or monitoring interval is scheduled.
  - If study treatment resumption is considered for patients who have experienced grade 3 increases in AST, ALT, or bilirubin with the first dose reduction and the Medical Monitor agrees, resume study treatment with the second dose level reduction (see table) when AST, ALT, or bilirubin returns to baseline value or grade 1.
- If grade 4 increases in AST, ALT, or bilirubin occur (e.g., AST or ALT to  $>20\times$  ULN or total bilirubin to  $>10\times$  ULN), patients must discontinue study treatment immediately and will not be re-challenged. They should be followed until resolution of abnormal liver function tests.

### 8.3 Other Non-Hematologic Toxicities

NCI standard toxicity criteria are included as Appendix C. Any grade 3 or 4 toxicity should be reported promptly to the Principal Investigator, and therapy should be held. Since such events are anticipated to be distinctly uncommon, dosage adjustment will be determined on an individual basis.

## 9.0 CRITERIA FOR RESPONSE

Tumor response will be determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Appendix D),<sup>47</sup> and PSA will be evaluated according to the Prostate-Specific Antigen Working Group's Guidelines.<sup>48</sup>

## 10.0 REASONS FOR DISCONTINUATION OF THERAPY

Patient will continue on therapy until

- Progression of disease
- Unacceptable toxicity
- Patient or treating physician wishes to stop

## 11.0 STATISTICAL CONSIDERATIONS

This study is intended to determine the efficacy of determining chemotherapy dose based on tumor burden. Time to tumor progression (TTP) is the primary endpoint. The study is designed to have at least 80% power to detect at least a 4-month increase in the median TTP found in the literature (16-24 months, two-sided type I error of 0.05), with an exponential distribution. We plan to enroll 224 patients.

assuming uniform accrual over time, no loss to follow-up, exponentially distributed death times, and the use of the exponential MLE test.

Each group will be examined separately in an independent post-hoc subgroup analysis using descriptive statistics. TTP may vary among treatment subgroups. The median PFS will be constructed for each subset. The 95% confidence intervals will describe the reliability of our results.

An interim safety analysis is planned after 56 patients (25%) have completed the first cycle of treatment. During this analysis, enrollment will be stopped, the DSMB will review the safety and toxicity information and make their recommendation, and the DSMB report will be given to the IRB for review prior to treatment of additional patients. For the interim analysis, the alpha spending function with O'Brien-Fleming type boundaries will be used to preserve the overall type I error rate for safety and effectiveness at the 0.025 level.

## **12.0 SAFETY MONITORING AND REPORTING**

The investigator will monitor each patient for clinical and laboratory evidence of adverse events on a routine basis throughout the study following the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. A link to the electronic version of the CTCAE can be found in Appendix C. Investigators must document their review of laboratory reports by initialing and dating each report, as well as addressing the clinical significance (for significant abnormalities). The investigator will assess and record any adverse event (serious and non-serious) in detail on the adverse event form including the date of onset, description, severity, time course, duration, outcome and relationship to the study drug from the time the patient signs the informed consent until 4 weeks after the patient has stopped study treatment.

### **12.1 Adverse Events**

All adverse events should be treated appropriately. Such treatment may include interruption or discontinuation of study drug, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention.

Information about common side effects already known about the study drugs can be found in the protocol (section 14) and respective package inserts. Two drugs in the study, doxorubicin and docetaxel, have known potential for non-overlapping cumulative toxicities (cardiac for doxorubicin and neuropathic for docetaxel). These are well known and are described in the package inserts. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

### **12.2 Adverse Event Definition**

An adverse event (AE) is defined as any unintended or undesirable, noxious, or pathological change, compared to pre-existing conditions, experienced by a patient during a clinical study or the follow-up period, regardless of relationship to study drug. Adverse events include:

- Suspected adverse drug reactions.
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity.
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug.

- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptomatology, or apparently unrelated illnesses.

### 12.3 Evaluating Adverse Events

Each adverse event will be evaluated to determine:

- the severity grade (mild, moderate, severe) or (grade 1-4)
- its relationship to the study drug(s) (suspected/not suspected)
- its duration (start and end dates or if continuing at final exam)
- action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
- outcome
- whether it constitutes a serious adverse event (SAE)

### 12.4 Determination of Severity

The severity of AEs will be assessed according to CTCAE, Version 4.0. If the AE is not defined in the CTCAE, the Investigator will determine the severity of an adverse event based on the following definitions:

- Mild (Grade 1): The AE is noticeable to the patient but does not interfere with routine activity. The AE does not require discontinuing administration or reducing the dose of the study drug.
- Moderate (Grade 2): The AE interferes with routine activity but responds to symptomatic therapy or rest. The AE may require reducing the dose but not discontinuing administration of the study drug.
- Severe (Grade 3): The AE significantly limits the patient's ability to perform routine activities despite symptomatic therapy. In addition, the AE leads to discontinuing administration or reducing the dose of the study drug.
- Life-Threatening (Grade 4): The AE requires discontinuing administration of the study drug. The patient is at immediate risk of death.

### 12.5 Determination of Relatedness

The Investigator will determine the relatedness of an adverse event with the study drug based on the following definitions:

#### **Not Related**

This category applies to those adverse events which, after careful medical consideration, are felt to be due to extraneous causes (disease, environment, etc.) that are not related to the administration of study drug.

#### **Probably Not Related** (must have first two bullets below)

This category applies to those adverse events, which, after careful medical consideration, are clearly felt unlikely to be related to the administration of the study drug. The relationship of an adverse event to the study drug can be considered probably not related if:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to

- It does not follow a known response pattern to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

**Possibly Related** (must have first two bullets below)

This category applies to those adverse events, which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug, but the possibility cannot be ruled out with certainty. The relationship of an adverse event to the study drug can be considered possibly related if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It follows a known response pattern to the suspected drug.

**Probably Related** (must have first three bullets below)

This category applies to those adverse events which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study drug. The relationship of an adverse event to the study drug can be considered probably related if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction in dose.\*
- It follows a known response pattern to the suspected drug.

**Definitely Related** (must have first three bullets below)

This category applies to those adverse events, which, after careful medical consideration, are felt to be related to the administration of the drug. The relationship of an adverse event to the study drug can be considered definitely related if:

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction in dose and, if applicable, appears upon rechallenge.\*
- It follows a known response pattern to the suspected drug.

\*There are exceptions when an adverse event does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists; e.g., 1) tardive dyskinesia, 2) fixed drug eruptions.

## 12.6 Serious Adverse Events

Information about all serious adverse events (SAEs) will be collected and recorded. A SAE is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:



- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

## 12.7 Reporting

The principal investigator has the obligation to report all serious adverse events to the IRB, DSMB and FDA according to their respective requirements. All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All SAEs should be reported to the DSMB within 5 days of first knowledge by the investigator. Deaths should be reported to the IRB within 24 hours of investigator knowledge. Any unexpected, serious, related adverse experiences should be reported within 7 days of investigator knowledge.

Any pregnancy that occurs during study participation should be reported. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

## 12.8 Unanticipated Problem Reporting

The Principal Investigator (PI) must notify the IRB of unexpected problems that might arise during the study within 7 days. The PI must make a judgment call regarding the expectedness and causality of the problem. Examples include:

- any adverse event which in the opinion of the PI is both unexpected and related and places patients or others at risk of harm
- Protocol deviation that harmed patients or placed patients in increased risk of harm
- A breach of confidentiality
- Change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol
- Information that indicates a change to the risks or potential benefits of the research

## 12.9 Interim Safety Analysis

Enrollment to the study will be halted after 56 patients (25%) have completed the first cycle of treatment. A summary of safety and toxicity information for these patients will be prepared and provided to the Committee for the Protection of Human Subjects (CPHS) at the University of Texas Health Science Center at Houston and Data Safety Monitoring Board (DSMB). In the absence of dose-limiting toxicities and safety observations that would prevent subsequent administration of the regimen in the opinion of the Investigator, in agreement with the CPHS and DSMB, enrollment to the study may continue.

In the presence of dose-limiting toxicities or safety observations that would prevent subsequent administration of the regimen in the opinion of the Investigator, subsequent enrollment to the study may continue at a reduced dose level only in agreement with the CPHS and DSMB.

## **13.0 DATA AND PROTOCOL MANAGEMENT**

### **13.1 Protocol Compliance**

Written informed consent must be obtained from the patient prior to study specific screening tests or procedures. Results of all baseline evaluations which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Investigator prior to enrollment of that patient. The investigator and/or research coordinator must see each patient prior to drug administration. All required interim and pre-treatment data should be available and the investigator must have made a designation as to tumor response and toxicity grade.

### **13.2 Data Collection**

Investigators or their designee must enter the data required by the protocol onto Case Report Forms (CRFs). A brief explanation for required but missing data should be recorded as a comment. The Principal Investigator is ultimately responsible for assuring that data entered into the CRFs are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. The Investigator will sign the CRFs to indicate that, to his/her knowledge, they are complete and accurate.

### **13.3 Database Management**

The data manager will review the CRF data entered by study staff for completeness and accuracy. Data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the study coordinator. The study coordinator will respond promptly to queries and make any necessary changes to the CRFs.

### **13.4 Site Monitoring**

To ensure that the protocol and Good Clinical Practices (GCP) are being followed and that study data are accurate, complete and reliable, the trial will be monitored by a Data Safety Monitoring Board (DSMB), Medical Monitor and CRA monitoring as specified in the Data Safety Monitoring Plan (DSMP) for the study and the DSMB's charter.

## **14.0 DRUG INFORMATION**

### **14.1 Degarelix**

#### **Pharmacology**



Degarelix is a third-generation gonadotropin-releasing hormone (GnRH) receptor antagonist that binds reversibly to the pituitary GnRH receptors, leading to a reduction in the release of gonadotropins, including testosterone. Degarelix causes a decrease in the plasma concentrations of luteinizing hormone and follicle-stimulating hormone and, subsequently, testosterone. Degarelix produces a faster suppression of testosterone and PSA with no testosterone surge or microsurges. This prevents the risk of clinical flare in advanced disease. In clinical studies, degarelix is usually well tolerated with limited toxicity and no evidence of systemic allergic reactions.

Plasma protein binding in vitro is ~90%. It is widely distributed throughout total body water. Degarelix undergoes peptide hydrolysis in the hepato-biliary system. According to in vitro studies, degarelix is not a substrate, inducer, or inhibitor of the CYP450 or p-glycoprotein transporter systems. No quantitatively significant metabolites of degarelix were detected in plasma after subcutaneous administration. Degarelix is not a substrate for the human CYP450 system. Degarelix is not an inducer or inhibitor of the CYP450 system in vitro. Therefore, clinically significant CYP450 pharmacokinetic drug-drug interactions are unlikely.

At least 20%-30% of a given dose of degarelix is excreted unchanged in the urine. A population pharmacokinetic analysis of data from the randomized study demonstrated that there is no significant effect of mild renal impairment (creatinine clearance [CrCL] 50-80 mL/min) on either the degarelix concentration or testosterone concentration. Data on patients with moderate or severe renal impairment is limited; therefore, degarelix should be used with caution in patients with CrCL <50 mL/min.

### **Supplier/How Supplied**

Degarelix is available as 120 mg and 80 mg powder for injection (Firmagon, Ferring Pharmaceuticals). It is supplied in a carton that contains the drug and supplies needed for preparation.

Starting dose – One carton contains:

- Two vials each with 120 mg of powder for injection
- Two prefilled syringes containing 3 mL of sterile water for injection, USP
- Two vial adapters
- Two administration needles

NDC 55566-8301-2, Maintenance dose – One carton contains:

- One vial with 80 mg of powder for injection
- One prefilled syringe containing 4.2 mL of sterile water for injection, USP
- One vial adapter
- One administration needle
- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

### **Dosage and Administration**

Degarelix administration requires an initial subcutaneous starting dose of 240 mg followed by a monthly subcutaneous maintenance dose of 80 mg every 28 days.

### **Solution Preparation**

#### **Starting dose**

Given as two 3-mL injections of 120 mg each. One vial of contains 120 mg of degarelix. Each vial is to be reconstituted with a prefilled syringe containing 3 mL of sterile water for injection; 3 mL is withdrawn to deliver 120 mg of degarelix at a concentration of 40 mg/mL

#### **Maintenance dose**

Given as one 4-mL injection. One vial contains 80 mg degarelix. Each vial is to be reconstituted with a prefilled syringe containing 4.2 mL of sterile water for injection; 4 mL is withdrawn to deliver 80 mg of degarelix at a concentration of 20 mg/mL

During preparation, keep the vial vertical at all times and do not shake the injection. Administer within 1 hour of reconstitution

### **Administration**

Degarelix solution is for subcutaneous use only. Do not administer intravenously. Administer subcutaneously in the abdominal region, choosing an area that will not be exposed to pressure. Injection sites should be varied.

### **Adverse Effects**

The most frequently reported adverse reactions were injection site reaction (35%-44%), hot sweats (26%), mild to moderate increases in transaminase and gamma-glutamyltransferase levels, and weight gain (9%-11%). For injection site reactions, the most frequently reported adverse reactions were pain (28%) and erythema (17%). These adverse reactions were mostly transient, of mild to moderate intensity, occurred primarily with the starting dose, and led to few discontinuations (<1%). Grade 3 injection site reactions occurred in  $\leq 2\%$  of patients receiving degarelix. Hepatic laboratory abnormalities were primarily grade 1 or 2 and were generally reversible. Grade 3 hepatic laboratory abnormalities occurred in <1% of patients. Post-marketing data indicates that hypersensitivity reaction may occur.

## **14.2 Ketoconazole**

### **Pharmacology**

Ketoconazole inhibits several adrenal enzymes required for steroid biosynthesis. It is a synthetic imidazole-derivative antifungal agent. When used in higher doses, ketoconazole has been shown to inhibit gonadal and adrenal steroidogenesis by disrupting the P-450-dependent enzyme system. Ketoconazole causes a rapid decrease in circulating androgens and is associated with significant responses in previously untreated prostate cancer. Dosages of 800-1200 mg daily have been reported to have a prolonged effect on testosterone synthesis and to interfere with corticosteroid synthesis by the adrenals.

Ketoconazole is rapidly absorbed from the GI tract. Oral bioavailability is similar following administration of tablets or suspension but is highest following administration of the ketoconazole solution. The bioavailability of oral ketoconazole depends critically on an acid pH in the stomach. Thus buffering the gastric pH with food or concomitant administration of drugs that increase gastric pH (i.e., antacids, H<sub>2</sub> blockers) decreases the bioavailability of ketoconazole.

### **Supplier/How Supplied**

IRB NUMBER: HSC-MS-14-0949

Ketoconazole is available as 200 mg tablets (Nizoral<sup>®</sup>, Janssen pharmaceuticals).

### **Dosage and Administration**

The recommended dose/schedule of ketoconazole for the treatment of prostate cancer is 400 mg orally three times daily with hydrocortisone replacement given in divided doses. Lower doses of ketoconazole have also been given (200 mg t.i.d.); however, the endocrine effects at this dose have not been found to be optimal.

### **Drug Interactions**

*Prolongation of the QT interval:* Many drugs, including astemizole (Hismanol<sup>®</sup>), terfenadine (Seldane<sup>®</sup>), omeprazole (Prilosec<sup>®</sup>), and cisapride (Propulsid<sup>®</sup>), have known interactions with inducers of P-450 such as ketoconazole. Rarely, serious cardiovascular effects, including arrhythmia, arrest, palpitations, syncope, and death have been reported in patients receiving ketoconazole concomitantly with these drugs.

*Antacids/H<sub>2</sub>-blockers:* Gastric acidity is necessary for the dissolution and absorption of ketoconazole; thus, any drug that decreases gastric acidity may decrease the absorption of ketoconazole.

### **Adverse Effects**

Ketoconazole is well tolerated in patients with adverse effects including mineralocorticosteroid excess secondary to CYP17 inhibition, which can be managed with oral hydrocortisone 20 mg in the morning and 10 mg in the evening. Other common side effects include diarrhea, stomach upset, and mild nausea/vomiting (50%).

*Endocrine:* Ketoconazole inhibits cortisol synthesis, particularly in patients receiving relatively high daily dosages or divided daily dosing of the drug. Patients taking 400 mg t.i.d. should be assumed to be adrenal suppressed and treated accordingly, with "stress doses" of corticosteroids given for serious intercurrent illness.

Bilateral gynecomastia with breast tenderness has occurred in some men during therapy with ketoconazole. Limited data suggest that gynecomastia occurs because ketoconazole decreases serum testosterone concentrations and to a lesser extent serum estradiol concentrations, resulting in an increased estradiol:testosterone ratio.

*Gastrointestinal:* The most frequent adverse reactions to ketoconazole are nausea and/or vomiting, which have been reported in 3-10% of patients. Abdominal pain, constipation, flatulence, GI bleeding, and diarrhea have also been reported. Adverse GI effects appear to be dose related, are reported less frequently when ketoconazole is administered with food, and usually subside with continued therapy.

*Hepatic effects:* Transient increases in serum AST (SGOT), ALT (SGPT), and alkaline phosphatase concentrations have been reported during ketoconazole therapy. Hepatotoxicity, which may be hepatocellular, cholestatic, or a mixed pattern of injury, has been reported rarely. Although ketoconazole-induced hepatotoxicity usually is reversible following discontinuance of the drug, recovery may take several months, and rarely death has occurred.

*Dermatologic effects:* Pruritus has been reported in ~2% of patients receiving ketoconazole. Rash, dermatitis, purpura, and urticaria have been reported in <1% of patients receiving ketoconazole, and in some cases these effects may have been manifestations of a hypersensitivity reaction to the drug.

### 14.3 Doxorubicin

#### Pharmacology

Doxorubicin (Adriamycin®) binds to nucleic acids, presumably by specific intercalation of the planar anthracycline nucleus with the DNA double helix. The anthracycline ring is lipophilic, but the saturated end of the ring system contains abundant hydroxyl groups adjacent to the amino sugar, producing a hydrophilic center. The molecule is amphoteric, containing acidic functions in the ring phenolic groups and a basic function in the sugar amino group. It binds to cell membranes as well as to plasma proteins. Doxorubicin has several proposed mechanisms of cytotoxic action, including DNA intercalation, covalent DNA binding, free radical formation, and inhibition of DNA topoisomerase I and II.

Doxorubicin is extensively metabolized in the liver and eliminated primarily in bile. Up to 40% of an administered dose is eliminated through the bile duct. Very small amounts of drug are eliminated through the urinary system. Doxorubicin is well tolerated. Common side effects include alopecia (92%), nausea (>10%) and vomiting (34%-37%), myelosuppression, cardiomyopathy, and secondary malignancies.

It is unclear which mechanisms play the biggest role in the cytotoxicity. However, it is clear that free radical formation, as a result of reactions with metal catalysts (e.g. iron, copper) and hydrogen peroxide is responsible for the cumulative cardiac toxicity seen with doxorubicin. Although commonly seen at total doses in excess of 500 mg/m<sup>2</sup>, it is clear that some patients have clinically significant cardiac dysfunction at substantially lower doses.

#### Supplier/How Supplied

Doxorubicin HCl is available as a solution for injection (2 mg/ml) or a lyophilized powder for reconstitution. Several manufacturers produce doxorubicin, with Adria Laboratories being the first company to market the drug (Adriamycin®). Various vial sizes are also available.

#### Solution Preparation

Lyophilized drug may be reconstituted with sterile water for injection, D5W, or normal saline. This solution does not need to be further diluted for administration.

#### Storage & Stability

The vials of lyophilized powder can be stored at room temperature, away from direct light, for at least 2 years. Commercial solutions need to be refrigerated. Reconstituted solutions are stable for long periods of time, but, if not used within 8 hours, need to be protected from light.

#### Administration of doxorubicin

Doxorubicin can be administered as an intravenous push, a slow infusion over several minutes to an hour, or as a continuous infusion for 24-96 hours. Different toxicities are associated with different methods of administration (see Adverse Effects below). In general, short infusions or bolus administration of doxorubicin cause more myelosuppression than continuous infusion.

continuous infusions of doxorubicin cause more mucositis than myelosuppression. There is evidence that prolonged infusion schedules are less cardiotoxic.

Doxorubicin is a vesicant and, if extravasated, can cause severe ulceration and necrosis. Therefore, it will be administered through a central line for infusion to prevent extravasation. Doxorubicin given peripherally as a slow infusion or as a bolus must be infused simultaneously with a running intravenous fluid through the same line. The nurse should check often for blood return when giving such infusions. Continuous infusions of doxorubicin should never be given through a peripheral i.v. site but requires a central line for infusion.

### **Drug Interactions:**

Doxorubicin is a major substrate of cytochrome P450 CYP3A4, CYP2D6, and P-glycoprotein (P-gp). Clinically significant interactions have been reported with inhibitors of CYP3A4, CYP2D6, and/or P-gp (e.g., verapamil), resulting in increased concentration and clinical effect of doxorubicin. Inducers of CYP3A4 (e.g., phenobarbital, phenytoin, St. John's Wort) and P-gp inducers may decrease the concentration of doxorubicin.

### **Adverse Effects**

*Hematologic:* Myelosuppression is the dose-limiting side effect for doxorubicin given as a short infusion or a bolus. Leukopenia is most common with a nadir of 10-14 days and recovery by day 21-28. Thrombocytopenia is less common (0.1%) and is rarely dose-limiting.

*Cardiac:* Doxorubicin is associated with acute and delayed cardiac toxicity. The acute effects on the cardiac system manifest as a rare pericarditis-myocarditis syndrome with or without electrophysiologic aberrations. The conduction abnormalities are generally transient and are not associated with severe morbidity or the need for dose modification. In contrast, the delayed cardiac toxicity is clearly dose related, generally associated with a cumulative dose of ~500 mg/m<sup>2</sup> of doxorubicin. Cardiac toxicity can take up to 10 years to manifest but is most often seen within 2-3 years following administration. The clinical syndrome presents as classic congestive heart failure and is usually irreversible but manageable. Patients with prior mediastinal irradiation ( $\geq 2000$  rad),  $>70$  years old, and a history of preexisting cardiovascular disease (e.g., myocardial infarction or long standing hypertension) are at increased risk for delayed cardiac toxicity secondary to doxorubicin.

Prolonged (24-96 h) infusions of doxorubicin have been shown to decrease the incidence of cardiac toxicity, allowing higher cumulative doses to be given without compromising cardiac function.

*Gastrointestinal:* Nausea and vomiting (N/V) are moderate to severe with doxorubicin, depending on the dose and the method of administration. N/V are more severe with bolus or short administration of doxorubicin compared to continuous infusions at the same dose. N/V usually begins 6-12 hours after the start of administration and can last for up to 48 hours after administration.

Mucositis is common with continuous infusions of doxorubicin. The lesions often follow the leukopenia, peaking at approximately day 10-14 and recovering by day 21-28. If the lesions are severe and traverse the entire GI tract, diarrhea might accompany them. Shortening the length of the infusion can be beneficial in preventing this occurrence. However, there is no evidence that shortening the length of the infusion can be beneficial in preventing this occurrence. However, there is no evidence that shortening the length of the infusion can be beneficial in preventing this occurrence. However, there is no evidence that shortening the length of the infusion can be beneficial in preventing this occurrence.

no effective treatments that will speed the healing process once the lesions are present. Leukocyte recovery is the only treatment that effectively heals the ulcers. Granulocyte colony-stimulating-factor (G-CSF, filgrastin, Neupogen<sup>®</sup>) has been shown, in a few studies, to decrease the incidence of mucositis.

*Vesicant reactions:* As mentioned earlier, doxorubicin is a vesicant and, if extravasated, will cause ulceration and necrosis, requiring surgical debridement and skin grafting for repair. This reaction is a slow process that may continue for several days. Immediate action is required to limit the tissue damage and prevent severe damage of underlying structures (e.g. tendons, nerves, muscles).

*Radiation recall:* Doxorubicin can cause reactivation of soft-tissue reactions in areas previously irradiated. The most sensitive area involved is the esophagus.

*Other:*

- Alopecia is nearly universal with doxorubicin but usually only includes the hair on the head and occasionally the eyebrows or eyelashes to a lesser degree.
- Doxorubicin is dark red and may impart an orange or pink color to the urine.
- Hyperpigmentation of nail beds and skin is occasionally seen with doxorubicin administration, and thin, fragile nails prone to superficial infection are commonly seen with weekly administration schedules, including that used in this protocol.
- Secondary malignancies have been reported post-market. Specifically, secondary acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) have occurred in patients receiving doxorubicin. Cumulative incidences were 0.2% at 5 years and 1.5% at 10 years in 2 separate trials of breast cancer patients who received an adjuvant doxorubicin-containing regimen. These leukemias generally develop within 1-3 years of treatment.
- Fertility may be affected secondary to therapy. Doxorubicin is toxic to male reproductive organs. Subjects may choose sperm banking if desired.

#### 14.4 Estramustine

##### Pharmacology

Chemically, estramustine (Emcyt<sup>®</sup>) is a combination of estradiol phosphate and nitrogen mustard linked via a carbamate at the C-3 position of estradiol. Estramustine was designed for use in advanced carcinoma of the prostate. Estramustine phosphate has bischloromethyl side chains and was presumed to act by chemical alkylation. However, the drug may not act as an alkylating agent. The basic steroidal structure also imparts weak estrogenic activity. Recent studies suggest that estramustine has antimicrotubule activity. The drug appears to bind to high- molecular-weight microtubule-associated proteins to promote microtubule disassembly. Estramustine can kill tumor cells in any phase of the cell cycle and causes cells to accumulate in metaphase.

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Estramustine sodium phosphate is a pro-drug administered orally. About 75% of orally administered estramustine phosphate is absorbed. After oral administration, it is rapidly converted to estramustine. The major active metabolite is another cytotoxic metabolite, estromustine. Estramustine and estromustine are metabolized to estradiol and estrone, respectively. The estrogens may cause the antigonadotropic effects reported (including decreased plasma concentrations of testosterone, dihydrotestosterone, gonadotropins, cholesterol, and 17-hydroxyprogesterone and increased concentrations of prolactin and cortisol). The compound is excreted as metabolites of both the alkylating and estrogenic moieties into the bile, urine, and feces. Non-renal excretion is the major route of elimination of estramustine. The terminal half-life of estramustine is reported to be ~20-24 hours in humans.

### **Supplier/How Supplied**

Estramustine phosphate is investigationally available as an injectable compound for intravenous use and commercially available as hard, off-white capsules containing 140 mg of drug as the disodium salt (12.5 mg sodium per capsule) from Roche Laboratories (Estracyte<sup>®</sup>) and Kabi Pharmaceuticals (Emcyt<sup>®</sup>). Long-term storage requires refrigeration at temperatures of 2-8°C. The commercially available capsules may be kept at room temperature for 24-48 h.

### **Administration**

In a randomized, three-way crossover study of 6 patients with prostate cancer, estramustine 420 mg administered with a low-calcium breakfast or milk significantly decreased the rate and extent of absorption. Thus, doses should be taken 1 h before or 2 h after meals; dairy products should not be taken with estramustine. The effect of antacid on estramustine absorption is not known; however, decreased drug absorption is possible.

### **Drug Interactions**

Because of the estrogenic effect, patients may have increased warfarin requirements while taking estramustine. Patients receiving a live virus vaccine may have increased risk of infection. Common side effects occurring at rate of >10% include mild nausea and, diarrhea, minor gastrointestinal upset, edema or exacerbation of peripheral edema, dyspnea, breast tenderness, and a transient increase in bilirubin, LDH, and AST.

### **Adverse Effects**

*Gastrointestinal:* Dose-limiting adverse effects of estramustine have generally consisted of extreme gastrointestinal toxicity. The nausea and vomiting from estramustine can occur soon after administration. Symptoms are generally transient and responsive to phenothiazines. A similar but delayed and often intractable gastrointestinal toxicity is rarely reported. This later presentation can occur up to 6-8 weeks after initiation of continuous therapy and usually necessitates drug discontinuance. Diarrhea is reported in 15-30% of patients.

*Cardiac:* Several patients with pre-existing cardiac disease have demonstrated increasing symptoms of congestive heart failure during estramustine therapy, presumably because of the salt-retaining effects of the estrogenic portion of the drug. Other rare cardiovascular complications include thromboembolism, ischemic effects, and cerebral effects. The incidence and severity are similar to those with estrogen treatment of prostate cancer.

*Endocrine:* Gynecomastia has been reported due to the estrogenic effects of estramustine.

## Pharmacology

Docetaxel (Taxotere) is a semisynthetic antimicrotubule agent. It is a taxane derivative similar to paclitaxel. Docetaxel is approximately 2 times as potent as paclitaxel and at least 5 times more potent against paclitaxel-resistant cells. It binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the inhibition of mitosis in cells.

In vitro, docetaxel is 94-97% protein bound. It is widely distributed throughout total body water. Docetaxel is primarily metabolized through the cytochrome p450 3A4 isoenzyme (CYP3A4) system and eliminated primarily through feces. Less than 6% is eliminated renally. Dose adjustments are required elevated serum bilirubin.

Common adverse effects include alopecia (56.3%-98%), fluid retention syndrome (6.5%-67%), myelosuppression, nausea (38%-81%), vomiting (22%-67%), stomatitis (19%-69%), cutaneous reactions (8%-41%), and hypersensitivity reaction (rare).

## How Supplied

Docetaxel is available as single-use vials of 20 mg/mL and 80 mg/4 mL (Taxotere, Sanofi-Aventis).

## Drug Interactions

Drugs that induce or inhibit CYP3A4 may lead to decreased efficacy or enhanced toxicity. These medications include cyclosporine, terfenadine, ketoconazole, and erythromycin.

## Adverse Effects

*Hematologic:* Myelosuppression is the dose-limiting side effect for docetaxel given as a short infusion or a bolus. Leukopenia is most common, with a nadir of 7, while thrombocytopenia is less common.

*Gastrointestinal:* Mucositis is most common. Other side effects include nausea, vomiting, stomatitis, and diarrhea.

*Fluid retention syndrome:* May be due to decreased colloid osmotic pressure of plasma followed by a capillary protein leakage.

*Neurologic:* Mild to moderate sensory neuropathy has been reported in patients treated with cumulative i.v. doses between 50 and 720 mg/m. The onset and severity varies between individuals. Dose reductions should be considered if severe neuropathic symptoms develop; treatment may need to be discontinued if symptoms do not resolve following a dose reduction.

*Hypersensitivity reaction:* This is a rare side effects and is attributed to the solvent Polysorbate 80. Dexamethasone administration for 3 days minimizes the incidence.

*Cutaneous reactions:* Commonly presents as a rash with or without itching. Docetaxel is continued for mild to moderate rash but may be discontinued if severe rash occurs despite dose adjustments.



## **Preparation and Administration Precautions**

Docetaxel is a cytotoxic anticancer drug, and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel solutions. The use of gloves is recommended. Please refer to Handling and Disposal section.

If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with the skin, immediately and thoroughly wash with soap and water.

If docetaxel concentrate, initial diluted solution, or final dilution for infusion should come into contact with mucosa, immediately and thoroughly wash with water.

Docetaxel for injection concentrate requires two dilutions prior to administration. Please follow the preparation instructions provided below. Note: Both the docetaxel for injection concentrate and the diluent vials contain an overfill.

### **A. Preparation of the Initial Diluted Solution**

1. If refrigerated, remove the appropriate number of vials of docetaxel for injection concentrate and diluent (13% ethanol in water for injection). Allow the vials to stand at room temperature for ~5 minutes.
2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for injection concentrate. If the procedure is followed as described, an initial diluted solution of 10 mg docetaxel/mL will result.
3. Gently rotate the initial diluted solution for ~15 seconds to assure full mixture of the concentrate and diluent.
4. The initial diluted docetaxel solution (20 mg docetaxel/mL) should be clear; however, there may be some foam on top of the solution due to the Polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

### **B. Preparation of the Final Dilution for Infusion**

1. Aseptically withdraw the required amount of initial diluted docetaxel solution (20 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3-0.74 mg/mL.

If a dose >200 mg of docetaxel is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel is not exceeded.

2. Thoroughly mix the infusion by manual rotation.

3. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel for injection initial diluted solution or final dilution for infusion is not clear or appears to have precipitation, these should be discarded.

The final docetaxel dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions.

Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene polyolefin) and administered through polyethylene-lined administration sets.

**Stability:** Unopened vials of docetaxel are stable until the expiration date indicated on the package when stored from 2-25°C (36-77°F) and protected from bright light. Freezing does not adversely affect the product.

### How Supplied

Docetaxel for injection concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in water for injection) vial. The following strengths are available:

#### Docetaxel 80 mg

Docetaxel 80 mg concentrate for infusion: 80 mg docetaxel in 2 mL Polysorbate 80 and diluent for docetaxel 80 mg; 13% (w/w) ethanol in water for injection. Both items are in a blister pack in one carton.

#### Docetaxel 20 mg

Docetaxel (docetaxel) 20 mg concentrate for infusion: 20 mg docetaxel in 0.5 mL Polysorbate 80 and diluent for docetaxel 20 mg; 13% (w/w) ethanol in water for injection. Both items are in a blister pack in one carton.

**Storage:** Store between 2°C and 25°C (36-77°F). Retain in the original package to protect from bright light.

Docetaxel initial dilution solution (10 mg docetaxel /mL) and final dilution for infusion solution (in either 0.9% sodium chloride solution or 5% dextrose solution) should be used within 4 hours (including the 1 hour administration) after preparation. However, the initial dilution solution is stable for 8 hours either at room temperature, 15-25°C (59-77°F), or stored refrigerated, 2-8°C (36-46°F).

**Handling and Disposal:** Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.<sup>1-7</sup> There is no general

agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

### **Weekly Dosing**

Protocols involving the weekly administration of docetaxel are currently utilizing 30-minute or 15-minute infusion times in addition to a 1-hour infusion period. This is due to the fact that the infusion solution volume (100 cc) for weekly docetaxel is generally less than that for every 3-week treatment (250 mL).

## **14.6 Management of Adverse Effects**

Any AE/SAE not listed in the CTCAE version 4.0 will be graded as follows

Severity of Event	
Grade	Definition
1	Mild: Symptoms which do not interfere with patient's daily activities
2	Moderate: Symptoms which may interfere with patient's daily activities
3	Severe: Events which interrupt patient's usual daily activities
4	Life-threatening or disabling
5	Death

Medically significant adverse events considered related to the study treatment by the investigator will be followed until resolved or considered stable.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these situations arises, the subject should be strongly encouraged to undergo medical supervision until symptoms cease or the condition becomes stable.

### **Management of Abnormal Laboratory Results**

All clinically important abnormal laboratory tests occurring during the study will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the investigator or until a diagnosis that explains them is made. The criteria for determining whether an abnormal laboratory test result should be reported as an adverse event are as follows:

1. Test result is associated with accompanying symptoms, and/or
2. Test result requires additional diagnostic testing or medical/surgical intervention (merely repeating an abnormal test, in the absence of any of the above conditions, does not meet criteria for reporting), and/or
3. Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Test result leads to any of the outcomes included in the definition of a serious adverse event, and/or

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5. Test result is considered to be an adverse event by the investigator

Any abnormal test result that is determined to be an error does not require reporting as an adverse event, even if it met one of the above conditions except for condition #4. Clinically significant laboratory results must be recorded in the patient's CRF.

### **Management of Cardiotoxicity**

Baseline echocardiograms and EKG will be conducted prior to therapy initiation. Additional ECG and echocardiograms will be obtained before each cycle of chemotherapy.

### **Management of electrolyte abnormalities**

Investigator should manage electrolyte abnormality as medically indicated per local standards

*Mucositis:* Stomatitis/oral mucositis/mouth ulcers should be treated using local supportive care. Examinations will describe whether the examination reveals mouth ulcers rather than general inflammation of the mouth. The paradigm below will be followed.

1. For mild toxicity (grade 1), use conservative measures such as non-alcoholic mouthwash or salt water (0.9%) mouthwash several times per day until resolution.
2. For more severe toxicity (grade 2, in which patients have pain but are able to maintain adequate oral alimentation, or grade 3 in which patients cannot maintain adequate oral alimentation), the suggested treatments are topical analgesic mouth treatments (i.e., viscous lidocaine 1%, diphenhydramine, and Mylanta® or Maalox [Aluminum Hydroxide | Magnesium Hydroxide | Simethicone]).
3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.
4. Oral antifungal agents such as fluconazole and nystatin may be used for oral candidiasis. Antiviral agents such as acyclovir should be avoided unless a viral infection is suspected.

### **Management of Nausea and Vomiting**

Investigator should manage nausea and vomiting as medically indicated per local standards.

### **Management of Anemia**

Investigator should manage anemia as medically indicated per local standards

### **Management of diarrhea**

The appearance of diarrhea attributed to treatment may be treated with loperamide

### **Management of Degarelix Adverse Effects**

#### *Injection site reaction*

After the initial and subsequent degarelix injections, subjects will place ice on the injection site to minimize local irritation and erythema.

#### *Hypersensitivity reactions*

Hypersensitivity reactions, including anaphylaxis, urticarial, and angioedema, have been reported post-marketing. In case of a serious hyp

immediately discontinued if the injection has not been completed and managed as clinically indicated.

#### *Hot flashes*

Hot flashes are frequently reported during the first 3 months, but with no overall difference over a 1-year period. Reporting during therapy initiation may be due to higher velocity of testosterone suppression. Increased body weight may predispose patients to hot flashes. Weight control may minimize the incidence.<sup>24</sup>

### **Management of Doxorubicin Adverse Effects**

#### *Vesicant extravasation, anthracycline-induced*

Infusion will be stopped and an initial dose of dexrazoxane (Totect®): 1000 mg/m<sup>2</sup> body surface area over 1-2 hours on day 1, maximum 2000 mg. Within 6 hours of extravasation, repeat the same dose 24 ± 3 hours on day 2, maximum 2000 mg, followed by a 500 mg/m<sup>2</sup> dose after 48 ± 3 hours on day 3, maximum 1000 mg.

### **Management of Docetaxel Adverse Effects**

#### *Fluid retention syndrome*

Severe fluid retention may occur; pretreatment with oral corticosteroids recommended prior to each dose; monitoring recommended with preexisting effusion. This AE occurs in 50-19% of patients treated with docetaxel every 3 weeks. It is characterized by weight gain, peripheral and/or generalized edema, pleural effusions, and ascites. Incidence is increased when total dose > 400 mg/m<sup>2</sup>. This may be due to decreased colloid osmotic pressure of plasma followed by a capillary protein leakage.

This AE is managed by premedication with dexamethasone 4-8 mg po bid x 3 days beginning 1 day prior to docetaxel administration. Patients developing new-onset edema, progression of existing edema, or another sign of fluid retention (e.g., 2 pound weight gain) are treated with oral diuretics such as triamterene/hydrochlorothiazide (one capsule orally [PO] once per day up to three times daily). If edema persists despite triamterene/hydrochlorothiazide therapy, give furosemide (40 mg PO daily) with potassium supplementation if needed. If after 2 weeks, furosemide 40 mg PO daily is not effective, furosemide (20 mg PO daily) plus metolazone (2.5 mg PO daily) with potassium supplementation if needed.

#### *Neurologic symptoms*

Neuropathy is usually mild and predominantly sensory. In most cases symptoms resolve after treatment discontinuation, but the toxicity can be severe and dose limiting, with symptoms that persist (and may even worsen) long after the last dose has been administered. Symptoms of neuropathy include paresthesia (skin sensation such as burning, prickling, itching, or tingling, with no apparent physical cause), weakness, feeling of heaviness in hands and feet, numbness and loss of ankle and knee jerk. These symptoms often result in clumsiness, loss of dexterity and unsteadiness of gait, and can be both painful and disabling.

Peripheral neuropathy is most commonly prevented by dose reduction. Whether the incidence of neuropathy is reduced by corticosteroid use remains unproven. There is also some anecdotal evidence that vitamin B6 may help to guard against neuropathy, and published preliminary evidence that glutathione may be protective. These measures require further study. There are no evidence-based management strategies for docetaxel-induced neuropathy

## **15.0 ETHICAL CONSIDERATIONS**

### **15.1 Ethical Compliance**

The study will be conducted in accordance with legal and regulatory (21 CFR 50, 56, 312 as applicable) requirements, as well as the general principles set forth in the Guidelines for GCP (ICH 1996) and the Declaration of Helsinki (World Medical Association 1996 and 2008).

The principal investigator is responsible for ensuring that all participating staff members are adequately trained and competent to perform his/her assigned tasks.

### **15.2 IRB Review**

Before implementing this study, the protocol, the proposed informed consent form, and other required information, must be reviewed and approved by a properly constituted Institutional Review Board (IRB). Any amendments to the protocol, other than administrative ones, must be reviewed and approved by this committee before implementation. If an immediate change to the protocol is implemented for safety reasons by the investigator, the IRB must be informed immediately. The study must be reviewed and approved at least annually as well.

### **15.3 Recruitment**

Recruitment typically occurs from patients treated at the Cancer Center. Recruitment may occur from patient self-referral from trials posted on ClinicalTrials.gov. If the investigator wishes to expand recruitment, advertisements will be reviewed and approved by the IRB prior to use.

### **15.4 Informed Consent**

The Investigator will be responsible for obtaining consent, documented on the Informed Consent Form (ICF) signed and dated by each patient or his/her legally authorized representative, prior to his/her participation in the study, in accordance with ICH GCP guidelines. The ICF will be written in non- technical language. The patient should read and be given as much time as they need to consider their participation before signing and dating it.

The investigator or study staff designee must explain to each patient the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Participation in the study and date of informed consent should be documented appropriately in the patient's files. The original ICF will be maintained in the research files and a copy must be maintained in the institution's medical records. The patient or his/her legally authorized representative will also be given a copy of the signed consent form.

### **15.5 Confidentiality**

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Patient names will not be supplied to third parties. A unique study accession number will be assigned to each patient on study and will be used on the CRFs. Identifiable data on any document (e.g., pathologist report) must be redacted before a copy of the document is supplied to third parties. The study coordinator will maintain a list to enable patients' records to be identified for verification purposes.

Study data stored electronically will be stored in zone 100, on password-protected, encrypted computers. Paper study data will be maintained by the study coordinator in the locked research offices.

#### **15.6 Publication of Study Results**

The investigator will assure that the key elements of this protocol will be posted in a publicly accessible database such as [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov). In addition, upon study completion and finalization of the study report the results of this study will be submitted for publication in scientific journals and/or scientific meetings. If the results of the study are published, the patient's identity will remain confidential.

#### **15.7 Retention of Documents**

To enable evaluations and/or audits from regulatory authorities or sponsors, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence in a secure storage facility.

Essential documents (written and electronic) should be retained for at least three (3) years after the completion of the study. The records should be retained by the investigator according to local regulations or as specified in the Clinical Study Agreement (CSA), whichever is longer.



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APPENDIX A: FACT-P Qualify of Life Scale

[REDACTED]

	[REDACTED]								
GP1	[REDACTED] .....	0	1	2	3	4			
GP2	[REDACTED] .....	0	1	2	3	4			
GP3	[REDACTED] [REDACTED]	0	1	2	3	4			
GP4	[REDACTED] .....	0	1	2	3	4			
GP5	[REDACTED] .....	0	1	2	3	4			
GP6	[REDACTED] .....	0	1	2	3	4			
GP7	[REDACTED] .....	0	1	2	3	4			

	[REDACTED]		Not at all	A little bit	Some- what	Quite a bit	Very much		
GS1	[REDACTED] .....	0	1	2	3	4			
GS2	[REDACTED] .....	0	1	2	3	4			
GS3	[REDACTED] .....	0	1	2	3	4			
GS4	[REDACTED] .....	0	1	2	3	4			
GS5	[REDACTED] .....	0	1	2	3	4			
GS6	[REDACTED] .....	0	1	2	3	4			
Q1	[REDACTED] <input type="checkbox"/>								
GS7	[REDACTED]								

[REDACTED]

[REDACTED]		Not at all	A little bit	Some- what	Quite a bit	Very much
GE1	[REDACTED] .....	0	1	2	3	4
GE2	[REDACTED] .....	0	1	2	3	4
GE3	[REDACTED] .....	0	1	2	3	4
GE4	[REDACTED] .....	0	1	2	3	4
GE5	[REDACTED] .....	0	1	2	3	4
GE6	[REDACTED] .....	0	1	2	3	4

[REDACTED]		Not at all	A little bit	Some- what	Quite a bit	Very much
GF1	[REDACTED] .....	0	1	2	3	4
GF2	[REDACTED] .....	0	1	2	3	4
GF3	[REDACTED] .....	0	1	2	3	4
GF4	[REDACTED] .....	0	1	2	3	4
GF5	[REDACTED] .....	0	1	2	3	4
GF6	[REDACTED] .....	0	1	2	3	4
GF7	[REDACTED] .....	0	1	2	3	4

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IRB APPROVAL DATE: 01/26/2016

#### APPENDIX B: ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead



## **APPENDIX C: NCI Common Terminology Criteria for Adverse Events (CTCAE)**

Safety and tolerability will be assessed according to Version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). An electronic version may be found at::

<http://ctep.cancer.gov/reporting/ctc.html>

In brief:

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL\*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL\*\*.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

A Semi-colon indicates \_or\_ within the description of the grade. A single dash (-) indicates a grade is not available.

### **Activities of Daily Living (ADL)**

\*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the tele-phone, managing money, etc.

\*\*Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.



## APPENDIX D: RECIST 1.1 Guidelines

Tumor response and progression will be defined according to RECIST 1.1 criteria. Electronic guidelines may be found at: <http://www.eortc.be/recist/documents/RECISTGuidelines.pdf>.

Response Evaluation Criteria in Solid Tumors (RECIST) Quick Reference:

### Eligibility

- Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint.  
**Measurable disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.  
**Measurable lesions** - lesions that can be accurately measured in at least one dimension with longest diameter  $\geq 20$  mm using conventional techniques or  $\geq 10$  mm with spiral CT scan.  
**Non-measurable lesions** - all other lesions, including small lesions (longest diameter  $< 20$  mm with conventional techniques or  $< 10$  mm with spiral CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.
- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

### Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Lesions on chest X-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- When the primary endpoint of the study is objective response evaluation, ultrasound (US) should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. US might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response when all lesions have disappeared.
- Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

#### **Baseline documentation of “Target” and “Non-Target” lesions**

- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

#### **Response Criteria**

##### **Evaluation of target lesions**

- |                             |   |
|-----------------------------|---|
| * Complete Response (CR):   | Disappearance of all target lesions   |
| * Partial Response (PR):    | At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD   |
| * Progressive Disease (PD): | At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions |
| * Stable Disease (SD):      | Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started                             |

##### **Evaluation of non-target lesions**

- |  |  |
|--|--|
| * Complete Response (CR):                  | Disappearance of all non-target lesions and normalization of tumor marker level                                  |
| * Incomplete Response/Stable Disease (SD): | Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits |

\* Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

- (1) Although a clear progression of —non target lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail and the progression status should be confirmed later on by the review panel (or study chair).

### Evaluation of best overall response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response/SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having —symptomatic deterioration. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

### Confirmation

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

### Duration of overall response

- The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or PD is objectively documented, taking as reference for PD the smallest measurements recorded since the treatment started.

### Duration of stable disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.
- The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

### **Response review**

- For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

### **Reporting of results**

- All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).
- All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.
- All conclusions should be based on all eligible patients.
- Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.
- The 95% confidence intervals should be provided.

**APPENDIX E: Schedule of Assessments:**

**Treatment Group 1: Prior prostatectomy or XRT with no radiographic involvement**

Protocol Activity	Pre-treatment		1 cycle = 8 wks								Cycles 2 & 3 D 1,8,15, 22,29,36	C2D5 0	Every 12 weeks after completion of chemo**
	-28 to -1	-7 to -1	C1D1	C1D8	C1D15	C1D22	C1D29	C1D36	C1D43	C1D50			
Informed Consent	X												
Physical exam		X								X		X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X
Height, weight		X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status		X								X		X	X
FACT-P QoL measurement											§		§
Inclusion/Exclusion criteria	X												
Complete metabolic profile		X	X	X	X	X	X	X	X	X	X	X	X
Electrolytes		X	X	X	X	X	X	X	X	X	X	X	X
CBC with diff. platelet count		X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, PTT		X								X	X	X	X
PSA		X								X		X	X
Testosterone		X											X
Chest X-Ray or CT	X											*	
Bone Scan	X											†	
CT or MRI abd	X											*	
MRI pelvis	X											*	



Protocol Activity	Pre-treatment		<i>1 cycle = 8 wks</i>								<i>Cycles 2 &amp; 3 D 1,8,15,22,29,36</i>	<i>C2D50</i>	<i>Every 12 weeks after completion of chemo**</i>
			<i>C1D1</i>	<i>C1D8</i>	<i>C1D15</i>	<i>C1D22</i>	<i>C1D29</i>	<i>C1D36</i>	<i>C1D43</i>	<i>C1D50</i>			
<i>Visit Name</i>	<i>-28 to -1</i>	<i>-7 to -1</i>											
ECG	(-180 to -1) X										***		
Echo	(-180 to -1) X										***		
PreTx observation			X	X	X	X	X	X			X		
IV Chemotherapy (3 cycles)			X	X	X	X	X	X			X		
ADT Tx (12 mos)			<i>C1D1 and monthly for total of 12 months (start date may be adjusted if patients received first dose prior to C1D1)</i>										

\*Repeat imaging if rise in PSA is >0.3 on 2 readings after maximum benefit

\*\* Every 12 weeks for the first 2 years, then every 6 months for the next 3 years, then annually

\*\*\*An ECG and echocardiogram will be obtained prior to each cycle of chemotherapy.

§ At completion of every cycle; 12 weeks after completion of chemotherapy; after completion of ADT; upon testosterone recovery.

† Repeat imaging if rise in PSA is >0.3 on 2 readings after maximum benefit and/or if abnormal at baseline.

**Schedule of Assessments:**

**Treatment Group 2: Nodal Involvement Only:      Treatment Group 3: Low Volume Bone Disease (4 Cycles)**

Protocol Activity	Pre-treatment		1 cycle = 8 wks								Cycles 2,3,4 D 1,8,15, 22,29,36	C2,4 D50	Every 12 weeks after completion of chemo**
	-28 to -1	-7 to -1	C1D1	C1D8	C1D15	C1D22	C1D29	C1D36	C1D43	C1D50			
Informed Consent	X												
Physical exam		X								X		X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X
Height, weight		X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status		X								X		X	X
FACT-P QoL measurement											§		§
Inclusion/Exclusion criteria	X												
Complete metabolic profile		X	X	X	X	X	X	X	X	X	X	X	X
Electrolytes		X	X	X	X	X	X	X	X	X	X	X	X
CBC with diff. platelet count		X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, PTT		X								X	X	X	X
PSA		X								X		X	X
Testosterone		X											X
X-Ray or CT Chest	X											*	
Bone Scan	X											†	
CT abd	X											*	
MRI pelvis*	X											*	
ECG	(-180 to -1) X										***		

Protocol Activity	Pre-treatment		1 cycle = 8 wks								Cycles 2,3,4 D 1,8,15, 22,29,36	C2,4 D50	Every 12 weeks after completion of chemo**
			C1D1	C1D8	C1D15	C1D22	C1D29	C1D36	C1D43	C1D50			
Visit Name	-28 to -1	-7 to -1											
Echo	(-180 to -1) X										***		
PreTx observation			X	X	X	X	X	X			X		
IV Chemotherapy (4 cycles)			X	X	X	X	X	X			X		
ADT Tx (18 mos)			C1D1 and monthly for total of 18 months (start date may be adjusted if patients received first dose prior to C1D1)										

\* Repeat imaging if rise in PSA is >0.3 on 2 readings after maximum benefit

\*\* Every 12 weeks for the first 2 years, then every 6 months for the next 3 years, then annually

\*\*\* An ECG and echocardiogram will be obtained prior to each cycle of chemotherapy.

§ At completion of every cycle; 12 weeks after completion of chemotherapy; after completion of ADT; upon testosterone recovery.

† Repeat imaging if rise in PSA is >0.3 on 2 readings after maximum benefit and/or if abnormal at baseline.

**Schedule of Assessments;**

**Treatment Group 4: Nodal with Bone Involvement; Treatment Group 5: High-Volume Bone/Visceral;**  
**Treatment Group 6: No Prior Definitive Local Therapy (5 Cycles)**

Protocol Activity	Pre-treatment		1 cycle = 8 wks								C 2,3,4,5 D 1,8,15, 22,29,36	C2,4 D50	Every 12 weeks after completion of chemo**
	-28 to -1	-7 to -1	C1D1	C1D8	C1D15	C1D22	C1D29	C1D36	C1D43	C1D50			
Informed Consent	X												
Physical exam		X								X		X	X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X
Height, weight		X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status		X								X		X	
FACT-P QoL measurement											§		§
Inclusion/Exclusion criteria	X												
Complete metabolic profile		X	X	X	X	X	X	X	X	X	X	X	X
Electrolytes		X	X	X	X	X	X	X	X	X	X	X	X
CBC with diff. platelet count		X	X	X	X	X	X	X	X	X	X	X	X
PT, INR, PTT		X								X	X	X	X
PSA		X								X		X	X
Testosterone		X											X
X-Ray or CT Chest	X											*	
Bone Scan	X											†	
CT abd	X											*	
MRI pelvis*	X											*	

Protocol Activity	Pre-treatment		1 cycle = 8 wks							C 2,3,4,5 D 1,8,15, 22,29,36	C2,4 D50	Every 12 weeks after completion of chemo**
			C1D1	C1D8	C1D15	C1D22	C1D29	C1D36	C1D43	C1D50		
Visit Name	-28 to -1	-7 to -1										
ECG	(-180 to -1) X										***	
Echo	(-180 to -1) X										***	
PreTx observation			X	X	X	X	X	X			X	
IV Chemotherapy (5 cycles)			X	X	X	X	X	X			X	
ADT Tx (24 mos)			C1D1 and monthly for total of 24 months (start date may be adjusted if patients received first dose prior to C1D1)									
Prostate Biopsy for viable cells	Group 6 only		At month 12									
Radiation therapy if viable cells	Group 6 only		At month 12									

\*Repeat imaging if rise in PSA is >0.3 on 2 readings after maximum benefit

\*\*Every 12 weeks for the first 2 years, then every 6 months for the next 3 years, then annually

\*\*\*An ECG and echocardiogram will be obtained prior to each cycle of chemotherapy.

§ At completion of every cycle; 12 weeks after completion of chemotherapy; after completion of ADT; upon testosterone recovery.

† Repeat imaging if rise in PSA is >0.3 on 2 readings after maximum benefit and/or if abnormal at baseline.